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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,668	08/28/2003	Alexei Brooun	SYR-ISPA-5001-C1	9129

32793 7590 03/31/2006

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EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 03/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/651,668	BROOUN ET AL.	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *11-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Claims 1-15 are pending in the instant application.

Restriction

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-10, drawn to a composition comprising a IspA protein crystal and methods for forming IspA protein crystal, classified in class 435, subclass 193.

II. Claims 11-15, drawn to a method of diffracting and solving structure of IspA protein, classified in class 702, subclass 27.

3. The inventions are distinct, each from the other because of the following reasons:

Group I and Group II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the product can be used for materially different process of using the product, such as using a protein crystal for soaking in the crystallization buffer with active site inhibitor to make an inhibitor bound protein crystals. Thus, Group I is patentably distinct from Group II.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Notice of Possible Rejoinder

4. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See

"Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Election

5. During a telephone conversation with David J. Weltz on 11 January 2006 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-10. Affirmation of this election must be made by applicant in replying to this Office action. Claims 11-15 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 11-15 are withdrawn from consideration as non-elected inventions. Claims 1-10 will be examined herein.

Priority

6. The application claims no priority for benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c).

Information Disclosure Statement

7. No information disclosure statement (IDS) has been filed in the instant application.

Compliance with Sequence Rules

8. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. ɜ 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a. The structural coordinates in Figure 3 teach an amino acid sequence since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the

sequence rules. Labeling using a SEQ ID No. must be inserted into the brief description of the drawings or into the Figure directly.

b. The "SEQ. ID No. 3" at the end of paragraph §00178 page 47 is not disclosed in the sequence listing. Appropriate correction is required.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID No.

Objections to the Specification

9. The specification is objected to because of the following informalities:

a. The specification is objected to because the title is not descriptive of elected claims. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The examiner suggests the following new title, for example:

---A crystalline composition of IspA, farnesyl pyrophosphate synthase---

b. The Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 08.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the full name of the enzyme (farnesyl pyrophosphate synthase) and the source species (*E. coli*) for completeness.

c. The specification contains statement "residues 1-299 (from SEQ. ID No.1), which corresponds to the full-length IspA from E. coli" on page 47 §00178. However, residues 1-299 does not contain full length IspA from E. coli. Clarification is required.

d. The specification has typographical errors in the specification page 47 §00180. The "SEQ. ID No. 1" is a protein sequence, however it is used as a gene sequence on page 47 in the instant specification; "gene encoding residues 544-935 (from SEQ. ID No.1)" and "nucleotide sequence 451-630 (SEQ. ID No. 1)". Appropriate correction is required.

e. The specification states "amino acid residues 694-753 (SEQ. ID No. 1)" on page 47 §00180. However, the range of residues 694-753 is not disclosed in the sequence.

The protein is 314 amino acids long in SEQ. ID No. 1. Appropriate clarification is required.

f. The specification has a typographical error in the specification page 48 §00180. The "SEQ. ID No. 2" is a DNA sequence, however it is used as protein sequence in the specification. Appropriate correction is required.

g. The specification has a typographical error in the specification page 48 §00180. The "SEQ. ID No. 2" is a DNA sequence, however it is used as protein sequence in the specification. Appropriate correction is required.

h. The specification cites "underlined" on page 48 §00180 to indicate the 6x-Histidine tag and rTev cleavage site sequences. However, the underline is not found in the sequence listing or drawings in the instant application. Clarification is required.

i. The specification cites "IspA protein samples (corresponding to SEQ. ID No. 1)" were used in the crystallization (see Example 2, page 49 §00183). However, the actual protein used in crystallization consists of residues 16-314 of SEQ ID No. 1. Appropriate clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 4 and 9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The phrases "a resolution greater than 3.0 Angstroms" in claims 4 and 9, are unclear as to the limitations they impart on the claimed subject matter or as to what said phrases encompass and one of ordinary skill in the art would not be reasonably apprised of the scope of the claimed crystals. It is well known in the art that the smaller the number (i.e. Angstroms), the higher the resolution. In this case, the term can be interpreted in the following two distinct ways: 1) a resolution of a number equal to or greater than 3.0 Å, which is a lower resolution or 2) a resolution of a number equal to or less than 3.0 Å, which is a higher resolution. Clarification is required.

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to any protein crystal and methods of making

crystal having a certain unit cell dimensions and at least 90% identity from residues 16-314 of SEQ. ID No. 1 (Claims 1 and 6) with optional additional limitations presented in individual, dependent claim form such as: at least 95% identity with residues 16-314 of SEQ. ID No. 1 (Claims 2 and 7), comprises consecutively of residues 16-314 of SEQ. ID No. 1 (Claims 3 and 8), a certain resolution (Claims 4 and 9), or a space group $P4_122$ (Claims 5 and 10). While the structure and function of one species of said genera of IspA are disclosed in the specification, the common structural characteristics of species that define said genera are not described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

Although, Example 2 describes the crystallization of *E. coli* IspA (residues 16-314 of SEQ ID No: 1) in the presence of ligands, the specification describes one species of an IspA crystal that falls within the instant genera of crystal. The crystal form described by Figure 2-6 is within the genera of Claims 1-5 based on their sequence, space group symmetry, unit cell dimensions (including error), and resolution.

While the claim language requires a function for the instant genera of crystals (that of IspA), the claims do not require, and the specification does not describe, any common characteristics that define the structure of the instant genera as a whole. In general, for a species of crystal to be adequately structurally described, the following must be adequately disclosed: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein (preferably a SEQ ID NO of all included residues) and any molecule bound to it), (2) the space group, and (3) the unit cell dimensions of the crystal. The species noted above has adequately met this burden by the description in the instant specification. However, the composition of the crystals encompassed by the breadth of the claims is not described because the exact molecule is not limited nor the space group and unit cell dimensions associated with this breadth of chemical composition described. In Claims 1 and 6, only unit cell dimensions are adequately described. The exact polypeptide sequence (SEQ ID No. 1), even with ligands in Claims, accompanied by the word "comprises" does not disclose the exact composition of the protein crystal in Claims 3 and 8. The space group disclosed in Claims 5 and 10 satisfies one adequate description but missing the other two descriptions as noted above. A singular chemical

composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). One of skill in the art would be unable to predict the structure of other members of the genera by virtue of the disclosed species of the instant disclosure. Therefore, claims drawn to the instant genera of crystals are also not adequately described.

12. Claims 6-10 are rejected under 35 U.S.C. 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to methods of using proteins in a suitable conditions and a precipitant for forming a protein crystal.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical Inc. v. Gen-Probe Inc.* (CAFC (2002) 63 USPQ2d 1609).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from *Enzo Biochemical* (see above).

Although, Example 2 describes a method of crystallizing *E. coli* IspA (residues 16-314 of SEQ ID No: 1) in the presence of ligands in seven different combinations, the specification disclose a description of only one species of an IspA crystallization that falls within the instant genera of crystallization that is within the genera of Claims 6-10 based on their sequence, space group symmetry, unit cell dimensions (including error), and resolution. A genus of proteins with a certain % sequence identity disclosed in

Claims cannot be adequately described by the species of *E. coli* IspA crystal disclosed by the instant specification. ~~Thus~~, The species of instant case does not correlate structure and function from species to genus.

KK 3/10/06

Because our understanding of crystallization mechanisms are still incomplete and the factors of macromolecular structure that are involved in crystallization are poorly understood, a method of the crystallization encompassed by the breadth of the claims is not adequately described by the method of crystallization disclosed in the specification.

In general, for a species of crystallization to be adequately structurally described, the following must be adequately disclosed: a composition of the protein solution and a precipitant solution used in crystallization (exact concentrations and volumes of all molecules used in the crystallization) must be described, including (1) the protein (preferably a SEQ ID NO of all included residues) (2) any ligand added (3) the precipitant solution). The species of crystallization noted in Example 2 of the instant specification have adequately met this burden. However, the crystallization encompassed by the breadth of the claims is not described.

A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). Therefore, the suitable condition disclosed in the specification to crystallize 16-314 of SEQ ID No. 1 cannot sufficiently describe a suitable condition of instant genus Claims.

13. Claim(s) 1-10 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method for preparing a protein crystal of a polypeptide consisting of residues 16-314 of SEQ ID No: 1 by crystallizing said polypeptide with ligands (IPP+Risedronate, see specification page 49), that results in a crystal having the space group $P4_122$ and the unit cell dimensions a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90^{\circ}$, does not reasonably provide enablement for all crystals and methods of preparation thereof as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The breadth of the claims: Claim 1 (claims 2-5 dependent therefrom) is so broad as to encompass any protein crystals with unit cell dimensions of +/- 5%, of a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90^{\circ}$ and at least a portion of the protein has at least 90% identity with residues 16-314 of SEQ. ID No. 1 (Claim 1) with optional additional limitations presented in individual, dependent claim form such as: at least a portion of the protein has at least 95% identity with residues 16-314 of SEQ. ID No. 1 (Claim 2), comprises consecutively of residues 16-314 of SEQ. ID No. 1 (Claim 3), a certain resolution (Claim 4), or a space group $P4_122$ (Claim 5). Claims 6 is also so broad as to encompass any methods for forming protein crystals with unit cell dimensions of +/- 5%, of a=88.80 Å, b=88.80 Å, c=174.99 Å and $\alpha=\beta=\gamma=90^{\circ}$ and at least a portion of the protein has at least 90% identity with residues 16-314 of SEQ. ID No. 1 (Claim 6) with optional additional limitations presented in individual, dependent claim form such as: at least a portion of the protein has at least 95% identity with residues 16-314 of SEQ. ID No. 1 (Claim 7), comprises consecutively of residues 16-314 of SEQ. ID No. 1 (Claim 8), a certain resolution (Claim 9), or a space group $P4_122$ (Claim 10).

The nature of the invention: The invention is related to protein crystals of *E. coli* IspA and methods of crystallization thereof. At the time of the invention, methods of

protein crystallization were well known in the art. However, the ability to crystallize a given protein was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: Regarding the claimed crystals, the state of the art at the time of the invention acknowledges a high level of unpredictability for making the full scope of claimed crystals. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "crystallization is usually quite difficult to achieve" (p. 375) and that "well ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Branden et al. further teaches that while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, "only a few small proteins have been determined to such high resolution" (p. 382, first full paragraph). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "the science of protein crystallization is an underdeveloped area" and "protein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (*Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable

physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as evidenced by Branden et al., which teaches that the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teaches that even small changes in the crystallization parameters, *e.g.*, pH, can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). Along these same lines, Wiencek (*Ann Rev Biomed Eng* 1:505-534) teaches that "protein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). In view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other IspA, farnesyl pyrophosphate synthase can be achieved using the crystallization parameters as set forth at p. 49 of the specification. Alternatively, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of residues 16-314 of SEQ ID No: 1 can be achieved using any crystallization parameters. Furthermore, the resolution "greater than 3.0 Angstroms" as disclosed in Claims 4 and 9 is not possible to predict by one skilled in the art because the resolution must be determined by X-ray crystallography.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses only a single working example of the claimed

crystal and the method of crystallization thereof. See specification at pp. 50, §00185. In Hosfield et al. (J.Biol.Chem. 279:8526-8529), the second *E. coli* IspA crystal with ligands IPP and DMASPP is known in the art within the scope of instant Claims. Other than these two working examples, the specification fails to provide guidance for altering the crystallization conditions for crystallizing proteins comprising residues 16-314 of SEQ ID No: 1 with an expectation of obtaining diffraction-quality crystals. Further, the specification fails to provide guidance for crystallizing residues 16-314 of SEQ ID No: 1 (*E. coli* IspA proteins) with other ligands disclosed in the instant specification set forth at pp. 50 or any other conditions with an expectation of obtaining diffraction-quality crystals.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, these methods are specific to a particular protein with two combinations of ligands as evidenced by the above teachings. Thus, a skilled artisan is left to experiment by a trial and error process to determine whether the disclosed crystallization conditions can be applied to crystallization of other proteins or whether residues 16-314 of SEQ ID No: 1 can be crystallized under a different set of crystallization parameters.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all methods and crystals as broadly encompassed by the claims, undue experimentation would be

necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

References of Record

14. The following references are cited to describe the closest prior art although these are not used in the art rejection herein: 1AIV, 1J4N, 1KYH, 1VDC are protein crystals within unit cell dimensions disclosed in Claim 1 and 6.

Conclusion

15. Claims 1-10 are rejected for the reasons identified in the numbered sections of the Office Action. Applicants must respond to the objections/rejections in each of the numbered sections in the Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alexander Kim
9 March 2006

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER